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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

BETA BLOKER TEDAVİSİ KRONİK OBSTRÜKTİF AKCİĞER HASTALIĞI OLAN HASTALARDA SAĞ VENTRİKÜLER FONKSİYONLARI İYİLEŞTİRİR

BETA BLOCKER THERAPY IMPROVES RIGHT VENTRICULAR FUNCTIONS IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ÖZET

AMAÇ: Kronik obstrüktif akciğer hastalığı (KOAH), mortalite ve morbidite oranı yüksek bir klinik tablodur. KOAH hastalarında kardiyak tutulum sık görülür. Bu hastalıkta beta bloker (BB) tedavisi, hastalığı ağırlaştıracağı endişesiyle çoğu zaman yeterli dozda kullanılamaz. Ancak aterosklerotik kalp hastalığı olan hastalarda BB ana ilaç tedavisidir. Bu çalışmada BB tedavisi alan KOAH'lı hastalarda sağ ventrikül (RV) fonksiyonlarını speckle tracking ekokardiyografi ile değerlendirildi.

GEREÇ VE YÖNTEM: Çalışmaya KOAH tanısı ile izlenen hastalar dahil edildi. Üç ay ve üzeri BB tedavisi alan hastalar grup-1 olarak oluşturuldu ve benzer demografik ve klinik özelliklere sahip hastalardan propensity skor eşleştirme (PSM) analizi ile kontrol grubu oluşturuldu. Hastaların temel demografik ve klinik özellikleri karşılaştırıldı ve BB tedavisinin etkileri incelendi.

BULGULAR: Toplam 75 çift (BB tedavisi alan 75 hasta ve benzer özelliklere sahip 75 hasta) çalışmaya dahil edildi. Hastaların yaş ortalaması 70±4,6 olup %73,7'si erkekti. PSM analizinden sonra; sağ ventriküler serbest duvar gerilimi (p <0,001), sağ ventriküler global longitudinal gerilimi (p <0,001), sağ ventriküler serbest duvar gerilim hızı (p: 0,001) ve sağ ventriküler global longitudinal gerilim hızı (p: 0,005) grup-1'de anlamlı olarak yüksekti.

SONUÇ: KOAH ve ateroskleroz, inflamasyon ve endotel disfonksiyonu gibi benzer yollara sahiptir ve KOAH hastalarında BB kullanımı sağ ventrikül fonksiyonlarını iyileştirmede olumlu bir etkiye sahip olabilir. Bu etki, geleneksel parametrelerden ziyade deformasyon analizinde gösterilebilir.

ANAHTAR KELİMELER: Sağ ventrikül, Gerilim, Gerilim hızı görüntüleme.

ABSTRACT

OBJECTIVE: Chronic obstructive pulmonary disease (COPD) is a clinical condition with a high mortality and morbidity rate. Cardiac involvement is common in COPD patients. In this disease, beta-blocker (BB) treatment could not be used in sufficient doses most of the time since it is thought that this treatment may aggravate the disease. However, BB is the main drug therapy in patients with atherosclerotic heart disease. In this study, right ventricular (RV) functions were examined using speckle-tracking echocardiography in COPD patients under BB therapy.

MATERIAL AND METHODS: Patients, who were followed up with the diagnosis of COPD, were involved in the study. Patients under BB treatment for three months or more were assigned to Group 1 and patients with similar demographic and clinical features to the control group by using propensity score matching (PSM) analysis. Baseline demographic and clinical features of patients were compared, and the effects of BB treatment were analyzed.

RESULTS: After PSM analysis, right ventricular free-wall global strain (p <0.001), right ventricular global longitudinal strain (p <0.001), right ventricular right ventricular free-wall global strain rate (p: 0.001), and right ventricular global longitudinal strain rate (p: 0.005) were found to be significantly higher in Group 1.

CONCLUSIONS: COPD and atherosclerosis have similar pathways such as inflammation and endothelial dysfunction, and the use of BB in COPD patients may have a positive effect on the improvement of right ventricular functions. This effect can be demonstrated by making use of the deformation analysis rather than conventional parameters.

KEYWORDS: Right ventricle, Strain, Strain rate imaging.

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INTRODUCTION

Atherosclerotic heart disease is one of the major causes of death and adverse events in developed countries. The plaque developing in the coronary artery and the changes in this plaque over time are the main reasons for the development of adverse events. Various methods (medical, percutaneous, or surgical) were introduced for its treatment (1, 2). Beta-blockers (BB) are one of the most widely used drugs in coronary artery disease (CAD) treatment. These agents reduce sympathetic system activation, prevent myocardial receptor downregulation, and reduce the risk of sudden death thanks to their antiarrhythmic effects. They also affect the heart rate and vasomotor tonus, thereby reducing blood pressure. In addition, they were shown to reduce adverse events in CAD thanks to their effects on different pathways such as improving autonomic nervous system balance, decreasing ischemia, and preventing myocardial fibrosis and apoptosis (3).

Chronic obstructive pulmonary disease (COPD) is a disease that is associated with an increased chronic inflammatory response of the lungs and is characterized by persistent and progressive airflow restriction. It is the third leading cause of death worldwide (4, 5). COPD is frequent in patients with heart failure (HF), especially in the elderly population. Despite this frequency, the method of treatment is controversial in the presence of COPD in patients with HF or CAD (6). Although BB therapies are recommended as the first-line treatment option in HF in current guidelines (7), BB therapy cannot be initiated or the dose cannot be increased effectively due to possible side effects in the presence of concomitant COPD. In this study, the effects of BB therapy on right ventricular (RV) functions in patients with COPD were examined by using speckle-tracking echocardiography.

MATERIAL AND METHODS

Study design

Patients, who were followed up for COPD, were involved in this study. The patients were divided into two groups considering the use of BB therapy. Patients given BB therapy were assigned to Group 1 and those with similar demographic and clinical characteristics as these patients to the control group (Group 2) by using the Propensity Score Matching (PSM) method. Patients using concomitant antiarrhythmic or inotropic agents, Newyork Heart Association (NYHA) group 4 patients, patients with insufficient echocardiographic data for deformation analysis, and patients receiving less than 3 months of BB therapy were excluded from the study.

Conventional Echocardiograph

As stated in the current American society of echocardiography (ASE) recommendations (8, 9), all echocardiographic examination was done in the left lateral decubitus position by using the Vivid 7 device (GE Health Care System). All patients were undergone standard echocardiographic examination including 2D and Doppler echocardiography and echo images were recorded at 50-70 fps for offline analysis. Most procedures were performed by a single accredited sonographer. The offline measurements were carried out by two experienced echocardiographers and checked by an expert imaging consultant cardiologist. Tricuspid Annular Plane Systolic Excursion (TAPSE) was measured by standard approach (10), and RV ejection fraction (RVEF) was calculated using the ellipsoid model (10, 11).

Two-dimensional deformation analysis

Measurements were obtained from apical four-cavity image recordings. The records were evaluated by two experienced cardiologists following current ASE recommendations (8,9) and using EchoPack software. After defining three reference points (RV apex, medial and lateral tricuspid ring), the software automatically traced the endocardial and epicardial borders. RV global longitudinal strain (RVGLS), RV global longitudinal strain rate (RVGL-SR), RV free-wall global strain (RVFGS), and RV free-wall global strain rate (RVFG-SR) were measured following the current guidelines **(Figure1)**. The same measurements were repeated one week later and interobserver and intra-observer variability were examined.

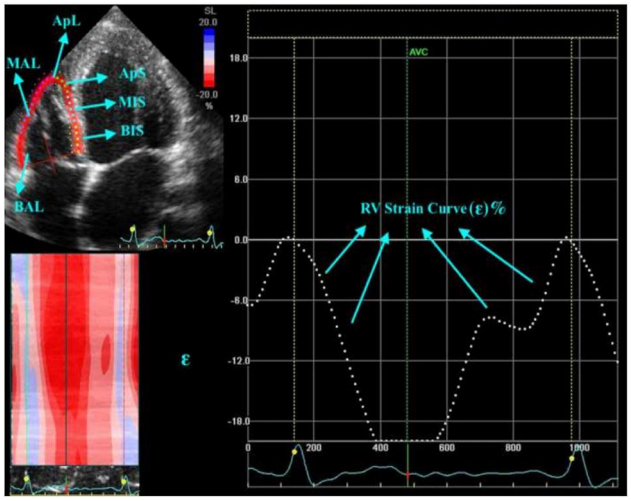

Figure 1: The echocardiographic method of right ventricular strain measurement, RV; right ventricle, MAL; mid-anterolateral, ApL; apicolateral, ApS; apical septum, MIS; mid- inferior septum, BIS; basal inferior septum.

Ethical Committee

The present study was designed retrospectively following the Helsinki Declaration and the local ethic committee approval was also obtained for this study (Afyonkarahisar Health Sciences University KAEK; date: 06.06.2022, number: 2022/07-84).

Statistical Analysis

Continuous variables were expressed as mean or median, whereas categorical variables were expressed as percentages. Kolmogorov Smirnov test was used to determine normality. Student T test or Man Whitney U test was used to compare continuous variables, and the X^2 test was used to compare categorical values. PSM analysis was conducted to balance the baseline demographic and clinical features of the participating patients. Propensity score (PS) was calculated for each patient by using a regression model. Analyzes were performed using SPSS Version 22 (Armonk, New York: IBM Corp). The statistical significance was set at p <0.05.

RESULTS

One hundred fifty patients were involved in the present study. Moreover, 74% of the participants were male and the mean age was found to be 69.5±4.6 years. Before the PSM analysis, diabetes, hypertension, and CAD were found to be significantly high in the groups **Table 1**. The baseline demographic and clinical features of the patients are shown in **Table 2**.

Table 1: Patient characteristics before and after propensity score matching

Variables	Before propensity score matching			After propensity score matching		
	Group-1	Group-2	P value	Group-1	Group-2	P value
Sex, (male)	76.1%	73.4%	0.621	75.4%	72.1%	0.621
Age (years)	69.7 ± 7.3	71.1 ± 7.7	0.683	69.7 ± 5.1	70.2 ± 7.3	0.683
DM (%)	37.1	31	0.04	35.2	33.6	0.578
HT (%)	35	30	0.007	33	31	0.129
CAD (%)	23	20.1	0.03	21.2	20.1	0.347
Smoking (%)	33	31	0.158	30	31	0.923

Abbreviations: DM, diabetes mellitus; HT, hypertension; CAD, coronary artery disease.

Table 2: Basal demographic and echocardiographic characteristics of the study groups

Variables	Group-1 (n = 75)	Group-2 (n = 75)	P value
RV diamater (mm)	42±3.6	44±5.3	0.082
LVEDD (mm)	46 ± 0.45	45 ± 0.91	0.831
LVESD, mm	26 ± 0.61	27 ± 0.32	0.549
E velocity (cm/s)	0.9 ± 0.2	0.8 ± 0.1	0.115
A velocity (cm/s)	0.7 ± 0.1	0.7 ± 0.1	0.732
e/e'	0.7 ± 0.2	0.8 ± 0.1	0.461
LA (mm)	45±6	45±6	0.792
sPAP (mm Hg)	40 ± 4.8	46.6 ± 9.7	0.014
IVS (mm)	1.1 ± 0.4	1 ± 0.3	0.572
LV-EF (%)	66.1 ± 5.9	64.8 ± 5	0.580
TAPSE(mm)	22(20-25)	23(21-27)	0.089
RV-EF	60.2 ± 4.4	60 ± 7.2	0.129
RV global longitudinal strain, (%)	17.6 ± 3.1	14.1 ± 3.6	<0.001
RV global longitudinal strain rate (s−1)	1.54(0.8-1.8)	1.28(0.8-1.5)	0.005
RV free wall global longitudinal strain (%)	19.2 ± 4.1	14.3 ± 3.7	<0.001
RV free wall global longitudinal strain rate (s−1)	1.69(0.9-1.96)	1.35(0.78-1.9)	0.001

Abbreviations: RV, right ventricle; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LA, left atrium; sPAP, systolic pulmonary arterial pressure; IVS, interventricular septum; RV-EF, right ventricular ejection fraction; LV-EF, left ventricular ejection fraction.

Even though there was no statistical difference between the groups, the right ventricular ejection fraction (RV-EF) was found to be higher in Group 1 (p=0.129), and the right ventricular diameter was higher in Group 2 (p=0.082). Pulmonary artery pressure (sPAB) was significantly higher in Group 2(p <0.001) (Table 2). Deformation analysis revealed that RVFWS (p <0.001), RVGLS (p <0.001), RVFW-SR (p=0.001), and RVGL-SR (p=0.005) were significantly higher in Group 1 (Table 2 and **Figure 2)**.

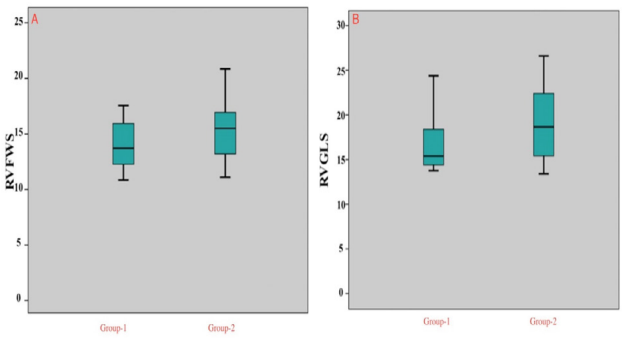

Figure 2: Box plot between BB usage and right ventricular free wall strain (A) and right ventricular global longitudinal strain (B)

DISCUSSION

The results achieved in the present study revealed that BB therapy has positive effects on RV function. Given these results, it can be implied that BB therapy could not worsen the clinical conditions of COPD patients and it has positive effects on RV functions. BB therapy is widely used for antianginal and antiarrhythmic purpo-

ses in atherosclerotic heart diseases. They block the negative effects of the sympathetic system on the cardiovascular system and reduce the risk of sudden cardiac death. Furthermore, they also contribute to reverse remodeling formation by causing beta receptor upregulation in heart failure and ultimately improve ejection fraction (1, 2, 12 - 14). The main limitation of BB therapy is the decrease in heart rate and the development of dyspnea. It is not recommended for use in patients with acute HF or NYHA group 4 since it will increase dyspnea. Similarly, asthma is another limitation for BB therapy (7).

Even though the effects of Renin–angiotensin–aldosterone system in CF patients, the knowledge regarding its effects on RV is still limited. Theoretically, an improvement in left ventricular functions would result in improvements in dolus pressures and pulmonary pressure, and a decrease may be seen in the right ventricular pressure. Besides that, the number of studies reporting this relationship is not sufficient. In particular, the knowledge on the sympathetic system and right ventricular functions is limited. The right ventricular functions are considered an important indicator of adverse events among CF patients. In previous studies carried out on rats, it was shown that BB treatment may result in improvement in the right ventricular functions and reduce dilatation (15 - 17). In a previous study carried out by Galves et. al (18) it was determined that BB treatment might have positive effects on both left ventricular and right ventricular remodeling among CF patients with low EF.

COPD is a clinical condition that results from alveolar-capillary oxygen transport disruption due to damage, inflammation, and hypersensitization in bronchial tissue caused by chronic exposure to cigarettes and allergens (5, 6). Although BB therapy is recommended for COPD patients with concomitant CAD, HF, or arrhythmia by current guidelines (7), BB therapy is not initiated or the dose is not increased due to the concern that it may worsen the patient's clinical condition. However, the use of BB in COPD patients was shown to yield a decrease in cardiovascular mortality in previous large-scale studies (12, 13, 19). Su et al. (10) reported that dose-dependent BB may be beneficial in COPD patients who started BB therapy due to heart failure. It was determined that there may be a decrease in the effect of bronchodilator therapy and airway hypersensitization with a decrease in forced expiratory volume during the use of non-selective BB (14). However, it was shown that selective beta-1 blockers do not cause adverse effects in those with mild-to-moderate airway obstruction (15 - 18). In a previous study, the development of right HF was shown to be reduced with bisoprolol treatment in patients with pulmonary hypertension (19).

Deformation analysis has recently been used to evaluate cardiac functions. It offers both fast and accurate diagnosis in the evaluation of cardiac functions, as well as low inter-observer variability. In addition, its clinical use is estimated to elevate thanks to its high repeatability and automatic tracking system. Even though most of the previous studies focused on left ventricular functions, it was shown to be effective in evaluating RV structure and functions and to be superior to traditional parameters (20 - 22).

Kalkan et al. (23) reported that deformation analysis is superior to traditional Doppler parameters in terms of the detection of RV deterioration in patients with mitral stenosis. Zhai et al. (24) found a significant relationship between RV performance and RVFWS in patients with pulmonary hypertension. RVFWS was associated with disease progression rate among patients with arrhythmogenic right ventricular dysplasia (25). PSM analysis is a regression model developed to reduce the bias rate. It is frequently used to increase the effectiveness of treatment and in clinical decision-making (26). In order to make clear inferences in clinical studies, the factors called confounders should be balanced as much as possible. In this context, PSM analysis is frequently used and it has started to be used in clinical studies more frequently (26). The present study revealed that RV functions were significantly better with BB therapy, and this result is consistent with the above-mentioned studies. Besides that, the determination of determining this relationship by using PSM analysis also contributes to the novelty of the present study.

The main advantage of deformation analysis is that this effect can be demonstrated by deformation analysis rather than traditional Doppler and echocardiographic parameters.

BB therapy could not worsen the clinical condition of COPD patients. Furthermore, it affects RV functions positively. In these patients, BB therapy can be started safely, and the dose can be increased safely to achieve maximum benefit.

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